1 TITLE PAGE

A Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Effect of Dose and Duration of Treatment of Itraconazole Administered as a Dry Powder for Inhalation (PUR1900) on Safety, Tolerability, and Potential Outcomes in Adult Patients with Asthma and Allergic Bronchopulmonary Aspergillosis

Study No: 601-0018

Name of Test Product:	PUR1900
Indication:	Asthma and Allergic Bronchopulmonary Aspergillosis
Study Registry Name and Number:	NCT05667662 EudraCT 2022-002289-33
Sponsor:	Pulmatrix, Inc. 36 Crosby Drive, Suite 100 Bedford, MA 01730
Sponsor's Responsible Medical Officer:	Christopher H. Cabell, MD MHS
Drug Development Phase:	2
Study Initiation Date:	First subject randomized: 01-Feb-2023
Date of Early Study Termination:	Last subject last visit: 27-Feb-2024
Report Date, Version:	31 May 2024, Version 1.0

This study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in US Federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Pulmatrix, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier:

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product
PUR1900</td></tr>
<tr><td>Name of Active Ingredient
itraconazole</td></tr>
<tr><td colspan="3">Title of Study:
A Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Effect of Dose and Duration of Treatment of Itraconazole Administered as a Dry Powder for Inhalation (PUR1900) on Safety, Tolerability, and Potential Outcomes in Adult Patients with Asthma and Allergic Bronchopulmonary Aspergillosis</td></tr>
<tr><td colspan="3">Study center(s):
Nineteen sites in the United States, Australia, France, and the United Kingdom.
Five sites enrolled patients.</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period (years):
Study Start: 01 February 2023
Study End: 27 February 2024</td><td>Phase of development:
2</td></tr>
<tr><td colspan="3">Objectives:
Primary: To evaluate the comparative safety and tolerability of 20 mg and 40 mg doses of PUR1900 in adults with asthma and allergic bronchopulmonary aspergillosis (ABPA).
Secondary: To estimate the magnitude of effect of daily administration of PUR1900 on potential outcome measures in adults with asthma and ABPA.
Exploratory: To assess for fungal resistance to Aspergillus fumigatus</td></tr>
<tr><td colspan="3">Endpoints:
Primary endpoints:
Incidence of TEAEs
Incidence of serious TEAEs
Safety assessments including Monitoring of FEV_1 throughout the study, Vital sign measurements, Physical examination findings, Clinical laboratory test results, 12-lead ECG findings
Secondary endpoints:
Change from baseline over time in FEV_1
Frequency of exacerbations
Change from baseline over time in ACQ-6 score
Change from baseline over time in AQLQ(S) 12+ score
Change from baseline over time in serum IgE levels
Exploratory endpoint:
Changes in sputum Aspergillus fumigatus antifungal susceptibility</td></tr>
</table>

Name of Sponsor/Company: Pulmatrix, Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product PUR1900		
Name of Active Ingredient itraconazole		

Methodology:

This was a randomized, double-blind, multicenter, placebo-controlled, parallel group study. The study consisted of a screening period of up to 28 days (4 weeks), a 112-day (16-week) treatment period, and a 56-day (8 week) observation period. Following screening and confirmation of eligibility, subjects were randomly assigned into 1 of 3 treatment groups (PUR1900 20 mg, PUR1900 40 mg, or placebo) using a 2:2:1 randomization allocation. A total of 7 scheduled visits were planned.

Safety of subjects was evaluated on an ongoing basis throughout the study. Reviews for AEs were performed at all remote and in-clinic assessments. Additionally, safety oversight was performed by the Medical Monitor, who reviewed the safety database in a blinded fashion monthly. An independent Data Monitoring Committee (DMC) was planned to review safety data after 15 subjects had received treatment with study drug; however, the DMC never met due to early study termination by the Sponsor after 8 subjects were enrolled.

On Day 1 of the 16-week treatment period, blood samples were obtained for baseline safety laboratory tests and for baseline serum immunoglobulin E (IgE). Baseline spirometry was conducted to measure forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC, and a baseline sputum sample was obtained for culture. Subjects were to complete the Asthma Control Questionnaire-6 (ACQ-6) and the Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[S] 12+). Training of subjects for use of the asthma monitoring device (AMD) to perform remote peak expiratory flow rate (PEFR) measurements and answering questions about asthma symptoms and rescue medication use was also conducted. On Day 14, study sites were to contact subjects remotely to perform a safety assessment and AMD review. On Days 28, 56, 84, and 112, subjects were to return to the study site and were dosed at the study site during those visits and in clinic spirometry was completed. On Day 168, subjects were to return to the study site for an end-of-study (EOS) visit for final assessments.

In accordance with the US Food and Drug Administration (FDA) Guidance for Industry "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" (August 1999), an abbreviated clinical study report was deemed appropriate for this study.

Number of patients (planned and analyzed):

Planned: 30

Enrolled: 8

Analyzed: 8

Note: the study was terminated early due to slow enrolment.

Diagnosis and main criteria for inclusion: Male or female subjects ≥18 years old with asthma and ABPA who met the diagnosis for ABPA based on the Modified International Society for Human and Animal Mycology (ISHAM) working group 2013 and 2021 criteria, and who currently had a serum IgE during screening ≥500 IU/mL.

Test product, dose, and mode of administration, batch number:

PUR1900, 20 mg itraconazole, dry powder inhalation.

Batch Numbers: 5076748, 5263080, 5504932

PUR1900, 40 mg itraconazole, dry powder inhalation

Batch Numbers: 5076750, 5263081, 5505052

Name of Sponsor/Company: Pulmatrix, Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	*(For National Authority Use Only)*
Name of Finished Product PUR1900		
Name of Active Ingredient itraconazole		

PUR1900 was administered via oral inhalation, once daily, using a dry powder inhaler (DPI) specific to the study (RS01 Monodose inhaler). To maintain the blind, all subjects were instructed to inhale the contents of 4 capsules per daily dose based on the subject's treatment group assignment, consisting of either: (1) two PUR1900 capsules and two placebo capsules or (2) four PUR1900 capsules.

Duration of treatment:

112 days (16 weeks) of treatment

Reference therapy, dose and mode of administration, batch number:

Placebo, dry powder inhalation.

Batch Numbers: 5265012, 5504931

Placebo was administered via oral inhalation, once daily, using a dry powder inhaler (DPI) specific to the study (RS01 Monodose inhaler). To maintain the blind, each subject was instructed to inhale the contents of 4 placebo capsules per daily dose. The placebo capsules were formulated to match the appearance of the powder in the PUR1900 capsule.

Criteria for evaluation:

Efficacy:

Data are presented in by-subject data listings only and include the following:

- Spirometry indices (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and FEV_1/FVC)
- Frequency of exacerbations
- Values and change from baseline at each visit for Asthma Control Questionnaire-6 (ACQ-6) score
- Values and change from baseline at each visit for Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[S] 12+) score by domain and overall
- Values and percent change from baseline at each visit for serum immunoglobulin E (IgE) levels

Safety:

Adverse events (AEs), Monitoring of respiratory parameters (FEV_1, FVC, PEFR, and FEV_1/FVC), laboratory test results (hematology, chemistry, urinalysis), vital signs, electrocardiograms, and physical examination findings.

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Name of Active Ingredient itraconazole		

Statistical methods:

All data listings and table summaries were generated using SAS version 9.4. Summaries were presented by treatment group, overall PUR1900, and overall in total. Continuous variables were summarized by the number of non-missing observations, mean, median, standard deviation (SD), and minimum and maximum values. Categorical variables were summarized by presenting the frequency and percent. Ordinal variables were summarized using categorical methods if the number of observed response categories was small (4 or fewer) and with mean, median, SD, minimum, and maximum otherwise.

Due to the early termination of the study, a limited number of summary tables and listings were generated. Descriptive statistics were used for the majority of data sets, without formal statistical testing. No adjustment for multiplicity was necessary. Efficacy endpoints (Randomized Set) were listed only for the Safety Analysis Set (i.e., all subjects who received any amount of study drug, and grouped as treated), summaries using descriptive statistics were provided for exposure to study drug (number of days of exposure) and overall treatment compliance. A summary of treatment-emergent adverse events (TEAEs) by system organ class and preferred term was presented for AE incidence and number of events reported. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. A listing was provided for all AEs, which also captures serious adverse events (SAEs), AEs of clinical interest (AECIs), AEs leading to death, and discontinuations due to AEs.

SUMMARY – CONCLUSIONS

Mild to moderate respiratory symptoms including asthma exacerbations and oropharyngeal pain, as well as mild arthralgia were the most common TEAEs reported overall. Asthma exacerbations were reported in 2 PUR1900-treated subjects, while oropharyngeal pain and arthralgia were reported in one subject each in PUR1900 and placebo-treated subjects. All other TEAEs were reported in one subject each, preventing any comparison across treatment groups. There were no SAEs or deaths. One subject in the placebo group discontinued treatment early due to moderate increased cough.

Transient declines in FEV_1 were observed as early as 5 minutes post-dose in 3 PUR1900-treated and 1 placebo-treated subject. These declines appeared to be reversible and were not associated with clinically significant respiratory symptoms.

No significant changes or abnormalities were observed in laboratory results, ECGs, physical examinations, or vital signs.

Due to the small number of subjects in the dosing groups, no conclusions can be drawn from these data.

Date of the report: 31 May 2024

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABPA	Allergic bronchopulmonary aspergillosis
ACQ-6	Asthma Control Questionnaire-6
AE	Adverse event
AECI	Adverse event of clinical interest
AMD	Asthma monitoring device
AQLQ(S) 12+	Standardized Asthma Quality of Life Questionnaire for 12 years and older
ATS	American Thoracic Society
BID	Twice daily
BMI	Body mass index
CRF	Case report form
DMC	Data Monitoring Committee
DPI	Dry powder inhaler
ECG	Electrocardiogram
EOS	End-of-study
EOT	End-of-treatment
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
IgE	Immunoglobulin E
ISHAM	International Society for Human and Animal Mycology
MedDRA	Medical Dictionary for Regulatory Activities
ms	millisecond
PEFR	Peak expiratory flow rate
PO	By mouth; orally
PT	Preferred term

Abbreviation	Definition
QTcF	QT interval corrected by the Fridericia formula
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan Description

This was a randomized, double-blind, multicenter, placebo-controlled, parallel group study. A total of approximately 30 subjects were planned to be enrolled; however, the study was terminated early by the Sponsor after enrollment of 8 subjects due to slower than anticipated enrolment rate. In accordance with the US Food and Drug Administration (FDA) Guidance for Industry "Submission of Abbreviated Reports and Synopses in Support of Marketing Applications" (August 1999), an abbreviated clinical study report was deemed appropriate for this study.

The study consisted of a screening period of up to 28 days (4 weeks), a 112-day (16-week) treatment period, and a 56-day (8 week) observation period. Following screening and confirmation of eligibility, subjects were randomly assigned into 1 of 3 treatment groups (PUR1900 20 mg, PUR1900 40 mg, or placebo) using a 2:2:1 randomization allocation. Subjects self-administered study drug (PUR1900 or placebo) via oral inhalation, using a dry powder inhaler (DPI) specific to the study (RS01 Monodose inhaler) once daily at approximately the same time of day, before noon. On Days 1, 28, 56, 84, and 112, subjects self-administered study drug at the study site under the supervision of site study personnel.

The study was performed in a double-blind manner. PUR1900 and placebo pre-metered capsules were supplied in identical packaging and were similar in appearance and performance/use characteristics to ensure the blind was maintained. Every subject received 4 capsules per daily dose, a combination of PUR1900 capsules and/or placebo capsules based on treatment group assignment.

Safety of subjects was evaluated on an ongoing basis throughout the study. Safety was monitored by FEV_1, FVC, and PEFR measurements obtained from in-clinic spirometry and in-home safety monitoring by subjects' use of an asthma monitoring device (AMD). Spirometry during study visits was conducted according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) standards, with a minimum of 3 and a maximum of 8 maneuvers (Graham et al. 2019). Additional safety measures included adverse events (AEs), exacerbations (and management thereof), laboratory test results (hematology, chemistry, urinalysis), vital signs, electrocardiograms, and physical examination findings.

Reviews for AEs were performed at all remote and in-clinic assessments. Additionally, safety oversight was performed by the Medical Monitor, who reviewed the safety database in a blinded fashion monthly. An independent Data Monitoring Committee (DMC) was planned to review safety data after 15 subjects had received treatment with study drug; however, the DMC never met due to early study termination by the Sponsor.

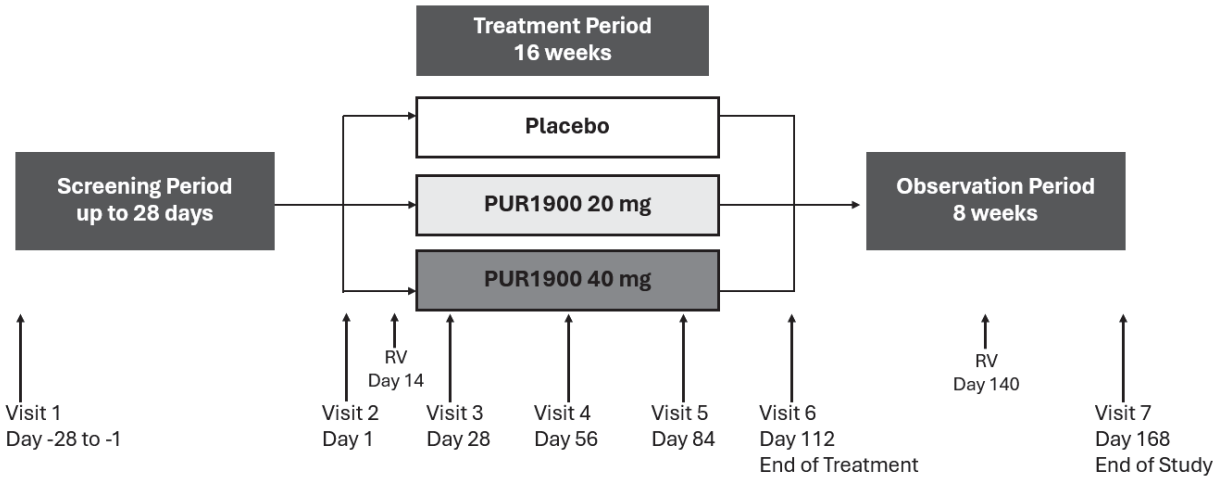
On Day 1 of the 16-week treatment period, blood samples were obtained for baseline safety laboratory tests and for baseline serum IgE. Baseline spirometry was conducted, and a baseline sputum sample was obtained for culture. Subjects were to complete the Asthma Control Questionnaire-6 (ACQ-6) and the Standardized Asthma Quality of Life Questionnaire for 12

years and older (AQLQ[S] 12+). On Day 14, study sites were to contact subjects remotely to perform a safety assessment and AMD review. On Days 28, 56, 84, and 112, subjects were to return to the study site and were dosed at the study site during those visits and in clinic spirometry was completed. The last day of treatment was Day 112.

Following the Day 112 visit, subjects entered an 8-week observation period. Subjects were to use the AMD to perform PEFR measurements and answer questions about asthma symptoms and rescue medication use. Subjects were to return to the study site for an end-of-study (EOS) visit on Day 168. The study design schematic is shown in Figure 1.

A list of planned study assessments and procedures is provided in the protocol (Appendix 16.1.1). A sample case report form (CRF) is provided in Appendix 16.1.2.

Figure 1 Study 601-0018 Study Schematic



Abbreviations: RV: remote visit

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The original protocol (Version 1.1, 07 JUL 2022) was amended twice throughout the study. One amendment was a UK-specific amendment to the protocol in response to Regulatory Agency questions applicable only to sites in the UK (Version 1.2 - UK). The protocol was amended globally to Protocol Version 2.0, 20 June 2023. Protocol Version 2.0 included all changes that were made in the UK specific amendment. The Summary of Changes is provided in Appendix 7 of Study 601-0018 Protocol Version 2.0.

9.8.2 Early Study Termination by the Sponsor

The study was terminated early by the Sponsor due to a slower than anticipated enrolment rate. All Investigators were notified on 08 January 2024 that the study was being terminated early. At that time, 5 subjects had completed the study as planned, 1 subject had discontinued treatment prematurely and continued in follow-up, and 2 subjects remained on treatment. Three subjects (one in each treatment group) that had not yet completed the treatment period follow-up returned for an End of Treatment Visit (Day 112/Visit 6) at their next scheduled visit, followed by a safety follow-up visit 28 days later. As a result, the treatment period follow-up was 84 days (versus 112 days), and the observation period was 28 days (versus 56 days) for these 3 subjects.

9.8.3 Changes in Planned Analyses

Due to the early termination of this study, the scope of the planned analyses was reduced as follows:

Since 8 subjects were enrolled, the following summaries were not included:

- The Full Analysis Set (defined as all randomized subjects who received at least 1 dose of study drug) (Protocol Section 8.6.2)
- Subgroup analysis for subjects who took a biologic agent during the study (Protocol Section 8.7)

Data were listed only for the following data sets:

- AEs (by treatment interval, by severity, by relationship to study drug, serious AEs, and AEs of clinical interest), vital signs, ECGs, physical examination, and clinical laboratory data (Protocol Section 8.8.1)
- Efficacy endpoints, including exacerbation data, questionnaire data, and actual value and change from baseline over time for FEV_1 and serum IgE (Protocol Section 8.8.2).
- Reasons for screen failure overall and by study site (Protocol Section 8.8.4.1)
- Prior medications (Protocol Section 8.8.4.2)

Data will be reported separately for fungal resistance to *Aspergillus fumigatus* (Protocol Section 8.8.3).

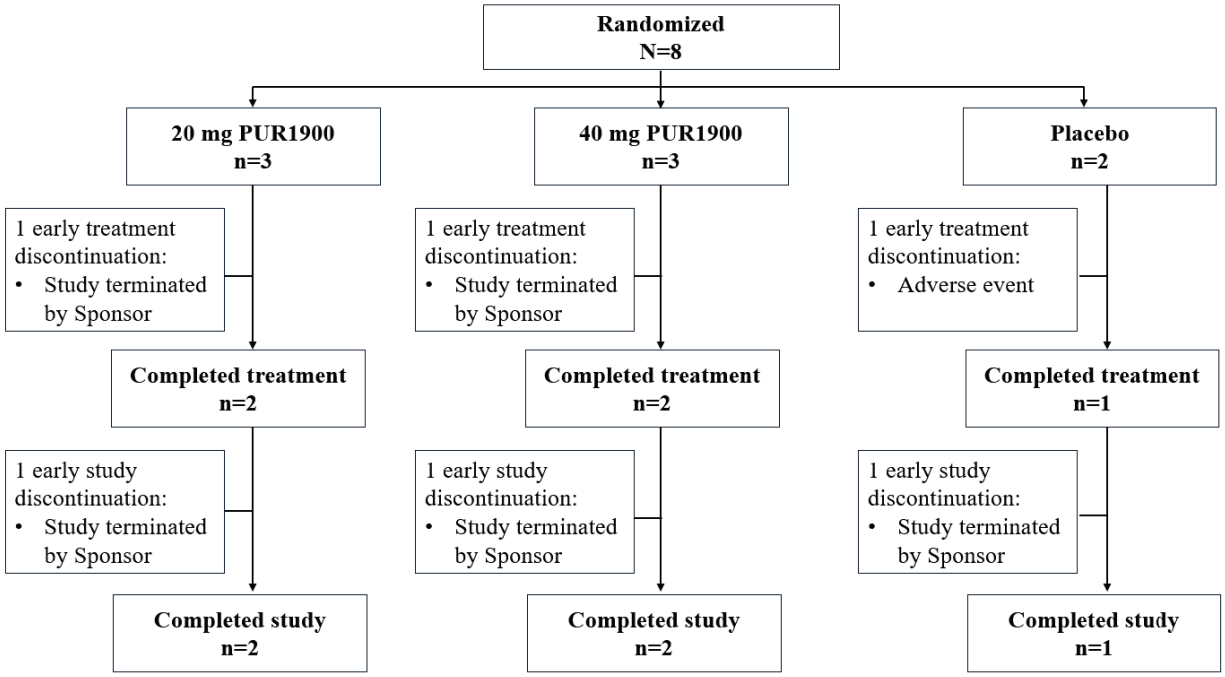
10 STUDY SUBJECTS

10.1 Disposition of Subjects

Subject disposition is summarized in Table 14.1.1. Overall, 8 subjects were enrolled prior to study termination: 3 subjects each were randomized to the PUR1900 20 mg and 40 mg treatment groups and 2 subjects were randomized to the placebo treatment group. Five (5) subjects completed the study in accordance with the protocol: 2 subjects each in the PUR1900 20 mg and 40 mg treatment groups and 1 subject in the placebo group. Of 3 subjects who discontinued treatment early, 1 subject in the placebo arm discontinued due to a treatment-emergent adverse event (TEAE) of moderate cough, and 2 subjects (1 in each PUR1900 treatment arm) discontinued due to the study termination by the Sponsor as described in Figure 2.

Individual subject disposition data are provided in Listing 16.2.1.1.

Figure 2 Subject Disposition



Source: Table 14.1.1

12 SAFETY EVALUATION

12.1 Extent of Exposure

The duration of study drug exposure ranged from 47 to 122 days overall. Mean study drug exposure was 107, 107, and 80 days for PUR1900 20 mg, PUR1900 40 mg, and placebo, respectively. The treatment period was truncated to 3 months for 3 subjects (1 in each treatment group) due to the Sponsor's decision to terminate the study. Of these 3 subjects, 1 subject in the

placebo group had already discontinued treatment early on Day 47 due to an adverse event resulting in lower mean study drug exposure overall in the placebo group.

Study drug exposure and overall compliance is summarized in Table 14.3.1.1.

Study drug exposure and compliance by subject is described in Listing 16.2.5.1.

12.2 Adverse Events (AEs)

All 8 randomized subjects were included in the Safety Analysis Set. A summary of TEAEs is presented in Table 14.3.1.2.

12.2.1 Brief Summary of Adverse Events

Overall, 7 subjects (87.5%) experienced ≥1 TEAE; all events were mild or moderate in severity. Three subjects (37.5%) experienced an AE that was assessed by the Investigator as related to study treatment and 1 subject (12.5%) experienced an AE assessed by the Investigator as related to the inhaler device. No serious TEAEs or TEAEs leading to death were reported. One (1) subject in the placebo group experienced a TEAE leading to treatment discontinuation: moderate cough which started on study day 44 and resolved on day 60 (Section12.3.1.1). One (1) subject in the PUR1900 40 mg group experienced moderate asthma (reported term: asthma exacerbation) TEAE categorized as an adverse event of clinical interest (AECI; Section 12.3.1.2).

12.2.2 Display of Adverse Events

All TEAEs (regardless of Investigator-assessed causality) are presented by system organ class (SOC) and preferred term (PT) in Table 1.

Table 1 Treatment-Emergent Adverse Events by Primary System Organ Class and Preferred Term Occurring in Subjects in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	PUR1900 20 mg (N = 3)		PUR1900 40 mg (N = 3)		PUR1900 Overall (N = 6)		Placebo (N = 2)		Overall (N = 8)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Subjects with any TEAE	3 (100)	8	2 (66.7)	4	5 (83.3)	12	2 (100)	10	7 (87.5)	22
Respiratory, thoracic, and mediastinal disorders	1 (33.3)	1	2 (66.7)	4	3 (50.0)	5	2 (100)	4	5 (62.5)	9
Asthma	1 (33.3)	1	1 (33.3)	1	2 (33.3)	2	0	0	2 (25.0)	2
Oropharyngeal pain	0	0	1 (33.3)	1	1 (16.7)	1	1 (50.0)	1	2 (25.0)	2
Cough	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Dyspnoea	0	0	1 (33.3)	1	1 (16.7)	1	0	0	1 (12.5)	1
Epistaxis	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Sputum discoloured	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Wheezing	0	0	1 (33.3)	1	1 (16.7)	1	0	0	1 (12.5)	1
Infections and Infestations	2 (66.7)	3	0	0	2 (33.3)	3	1 (50.0)	1	3 (37.5)	4
Viral infection	1 (33.3)	2	0	0	1 (16.7)	2	0	0	1 (12.5)	2
Bacterial disease carrier	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Influenza	1 (33.3)	1	0	0	1 (16.7)	1	0	0	1 (12.5)	1
Musculoskeletal and connective tissue disorders	1 (33.3)	2	0	0	1 (16.7)	2	1 (50.0)	1	2 (25.0)	3
Arthralgia	1 (33.3)	1	0	0	1 (16.7)	1	1 (50.0)	1	2 (25.0)	2
Back pain	1 (33.3)	1	0	0	1 (16.7)	1	0	0	1 (12.5)	1
Gastrointestinal disorders	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Nausea	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
General disorders and administration site conditions	1 (33.3)	1	0	0	1 (16.7)	1	0	0	1 (12.5)	1
Influenza like illness	1 (33.3)	1	0	0	1 (16.7)	1	0	0	1 (12.5)	1

System Organ Class Preferred Term	PUR1900 20 mg (N = 3)		PUR1900 40 mg (N = 3)		PUR1900 Overall (N = 6)		Placebo (N = 2)		Overall (N = 8)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Immune system disorders	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Hypersensitivity	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Investigations	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Sputum abnormal	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Nervous system disorders	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Headache	0	0	0	0	0	0	1 (50.0)	1	1 (12.5)	1
Skin and subcutaneous tissue disorders	1 (33.3)	1	0	0	1 (16.7)	1	0	0	1 (12.5)	1
Rash pruritic	1 (33.3)	1	0	0	1 (16.7)	1	0	0	1 (12.5)	1

Subjects are counted once at the 'Any Reported' level and within each system organ class and preferred term reported.
Percentages are based on the number of subjects in the Safety Analysis Set.
Footnotes: Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1
Abbreviations: m = number of adverse events; n = number of subjects with at least one adverse event; TEAE = treatment-emergent adverse event.
Source: Table 14.3.1.3

12.2.3 Analysis of Adverse Events

There were 22 TEAEs reported in 7 subjects. Overall, the most common TEAEs by SOCs were respiratory, thoracic, and mediastinal disorders, as well as infections and infestations. The only PTs reported in more than 1 subject overall were asthma (n=2), oropharyngeal pain (n=2), and arthralgia (n=2). All TEAEs were mild (n=17) or moderate (n=5) in severity. Overall, 3 subjects had at least 1 TEAE (4 TEAEs in total) assessed by the Investigator as related to treatment:

- mild wheezing and mild dyspnoea were deemed definitely related to treatment in Subject 102-001 in the PUR1900 40 mg group,
- mild pruritic rash was deemed possibly related to study drug in Subject 101-002 in the PUR1900 20 mg group, and
- moderate cough was deemed possibly related to study drug and possibly related to the inhaler device in Subject 107-001 in the placebo group.

12.2.4 Listing of Adverse Events by Subject

Adverse events are listed by subject in Listing 16.2.7.1.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths or serious adverse events (Table 14.3.1.2).

Subject 107-001 in the placebo group experienced a TEAE leading to treatment discontinuation: a moderate cough which started on Day 44 and resolved on Day 60 without any concomitant or additional treatment (Section 12.3.1.1 and Table 14.3.2.1).

One AECI was reported in Subject 102-001 in the PUR1900 40 mg group: a moderate exacerbation deemed unlikely related to study drug started on Day 52 and resolved on Day 65 with concomitant oral prednisone (Section 12.3.1.2 and Listing 16.2.7.1).

12.3.1 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Brief narratives are included for all 8 subjects regardless of occurrence of SAEs, TEAEs leading to treatment discontinuation, or AECIs.

12.3.1.1 Narrative of Adverse Event Leading to Treatment Discontinuation

Subject ID: 107-001

An 82-year-old white male subject was randomly assigned to the placebo arm on 26 Oct 2023. His height was 178.1 cm, weight was 85.9 kg, and body mass index (BMI) was 27.1 kg/m^2 at baseline.

The subject's concomitant medications and concurrent medical conditions included salbutamol, umeclidinium bromide, budesonide/formoterol fumarate, and tezepelumab for asthma with

Stage 5a ABPA; fluticasone propionate for allergic rhinitis and seasonal allergy; atorvastatin for hypercholesterolemia; apixaban for atrial fibrillation; levothyroxine for hypothyroidism; latanoprost and dorzolamide for glaucoma; omeprazole for gastroesophageal reflux disease (GERD); hydrochlorothiazide for peripheral edema; chlordiazepoxide for abdominal rigidity. Other concurrent medical conditions included prostatomegaly and arthralgia.

On Day 34 (Unscheduled Visit to collect spirometry and ECG that were not done at Day 28 Visit due to a software update preventing use of spirometry equipment), a reduction in FEV_1 of >20% occurred at 5 minutes post-dose relative to pre-dose baseline. The subject was asymptomatic, and no intervention was required; however, per protocol, study drug was held for at least 7 days (Day 35 to Day 42). On Day 43, study drug administration was conducted in the clinic. At this unscheduled visit, reductions from pre-dose baseline of FEV_1 of >10% occurred at 30 minutes and 1 hour post dose; however, no reduction of FEV_1 >20% occurred after the dose and the subject was asymptomatic; thus, remote self-administration of study drug was resumed.

On Day 44, the subject had a non-serious TEAE of moderate increase cough after inhalation of study drug. The event was assessed by the investigator as possibly related to both the study drug and the inhaler device. Asthma was also suggested as an alternative cause of the TEAE. Study drug administration was withdrawn on Day 47 (11 Dec 2023) due to the TEAE of increase cough and the subject continued in follow-up per the protocol. The event resolved on Day 60 without any concomitant therapy or additional treatment. During study participation, the subject had 6 instances of post-dose reductions >10% relative to pre-dose baseline. The subject's spirometry parameter pre- and post-dose values at each visit are presented in Table 2.

There were no clinically significant findings in vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram.

Due to study termination by Sponsor, the subject completed the Day 112/EOT assessments early on Day 85 (18 Jan 2024) and did not complete the Day 84 Visit. The subject discontinued the study early and completed the Day 168/EOS assessments on Day 119 (21 Feb 2024) due to study termination by Sponsor.

In summary, Subject 107-001 had 1 TEAE which was assessed by the investigator as related to study drug and inhaler device and resulted in discontinuation of study drug. Six (6) instances of post dose FEV_1 exceeding a 10% reduction from pre-dose values occurred during study participation with 1 instance of a >20% reduction. These declines were reversible and were not associated with clinically significant respiratory symptoms.

Table 2 Subject 107-001 Spirometry Parameters by Visit

Parameter	Visit	Day 1	Day 28*	Unsch	Unsch	Day 56	Day 112	Day 168 or EOS
	Study Day	**1**	**27**	**34**	**43**	**57**	**85**	**119**
FEV_1 (L)	Pre-dose	1.94	-	1.77	1.79	1.78	1.70	1.68
	Post-dose 5 min	1.70	-	1.40	1.64	-	-	-
	%CFPDV	-12.4	-	-20.9	-8.4	-	-	-
	Post-dose 30 min	1.70	-	1.60	1.59	-	-	-
	%CFPDV	-12.4	-	-9.6	-11.2	-	-	-
	Post-dose 1 h	1.93	-	1.56	1.59	-	-	-
	%CFPDV	-0.5	-	-11.9	-11.2	-	-	-
	Post-dose 2 h	1.77	-	-	-	-	-	-
	%CFPDV	-8.8	-	-	-	-	-	-
	Post-dose 4 h	1.78	-	-	-	-	-	-
	%CFPDV	-8.2	-	-	-	-	-	-
FVC (L)	Pre-dose	3.74	-	3.28	3.22	3.31	3.17	3.23
	Post-dose 5 min	3.18	-	2.76	3.12	-	-	-
	Post-dose 30 min	3.31	-	3.00	3.09	-	-	-
	Post-dose 1 h	3.79	-	2.93	2.95	-	-	-
	Post-dose 2 h	3.68	-	-	-	-	-	-
	Post-dose 4 h	3.30	-	-	-	-	-	-
FEV_1/FVC	Pre-dose	0.52	-	0.54	0.56	0.54	0.54	0.52
	Post-dose 5 min	0.53	-	0.51	0.53	-	-	-
	Post-dose 30 min	0.51	-	0.53	0.51	-	-	-
	Post-dose 1 h	0.51	-	0.53	0.54	-	-	-
	Post-dose 2 h	0.48	-	-	-	-	-	-
	Post-dose 4 h	0.54	-	-	-	-	-	-

%CFPDV=percent change from pre-dose to post-dose within a given visit; EOS=end of study; FEV_1=forced expiratory volume in 1 second; h=hour; min=minutes. FVC=forced vital capacity. *Spirometry was not performed at Day 28 visit due to software update preventing use of equipment; subject returned to complete spirometry at unscheduled visit on Day 34. '-' denotes not determined. Shaded cells across all spirometry parameters represent the timepoints for which reductions in FEV_1 were ≥10%.
Source: Listing 16.2.6.5

12.3.1.2 Narrative of Adverse Event of Clinical Interest (AECI)

Subject ID: 102-001

A 49-year-old white male subject was randomly assigned to the PUR1900 40 mg treatment arm on 01 Feb 2023. His height was 177.8 cm, weight was 98.7 kg, and BMI was 31.2 kg/m^2 at baseline.

The subject's concomitant medications and concurrent medical conditions included salbutamol, fluticasone furoate/umeclidinium bromide/vilanterol trifenatate, and dupilumab (started on Day 90) for asthma with Stage 2 ABPA, loratadine for perennial allergies, and finasteride for male pattern baldness.

On Day 34, the subject had a non-serious TEAE of mild wheezing. Study drug administration was not changed. The event was assessed by the investigator as definitely related to the study drug and unrelated to the inhaler device. No alternate causality was provided. The event resolved on Day 34.

On Day 52, the subject had a non-serious TEAE of moderate asthma (reported term: asthma exacerbation). Study drug administration was not changed. The subject was prescribed oral prednisone 20 mg once daily for 5 days (Days 57-61) for the asthma exacerbation TEAE. As assessed by the investigator, the event was an adverse event of clinical interest (AECI) and was unlikely related to study drug or the inhaler device. No alternate causality was provided. The event of moderate asthma exacerbation resolved on Day 65.

On Day 71, the subject had a non-serious TEAE of mild shortness of breath. Study drug administration was not changed. The event was assessed by the investigator as definitely related to the study drug and unrelated to the inhaler device. No alternate causality was provided. The event resolved on Day 71 with the use of concomitant salbutamol. On Day 90, the subject was initiated on dupilumab for treatment of asthma and remained on dupilumab for the remainder of the study. The subject missed study drug administration on Day 90 through Day 100 because the subject was erroneously withdrawn from the study after starting dupilumab. The subject resumed study drug on Day 101.

There were no clinically significant findings in vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram.

During study participation, there were 2 instances of post-dose reductions in FEV_1 of ≥10% relative to pre-dose baseline, both occurring at the 5-minute post-dose timepoint on Days 1 (−31.4%) and 112 (−15.5%). These declines were reversible and were not associated with clinically significant respiratory symptoms. The subject's spirometry parameters pre- and post-dose at each visit are presented in Table 3.

The subject completed the treatment period on Day 113 (24 May 2023). The subject completed study participation on Day 226 (14 Sep 2023), 51 days beyond the visit window allowed for the End of Study Visit due to scheduling challenges at the site.

In summary, Subject 102-001 had one AECI, a moderate asthma exacerbation deemed unlikely related to study drug, as well as two other mild respiratory symptom TEAEs deemed definitely related to study drug: wheezing and shortness of breath. Transient post-dose FEV_1 reductions were observed on Day 1 and Day 112; however, the subject remained asymptomatic and FEV_1 trended back to baseline thereafter.

Table 3 Subject 102-001 Spirometry Parameters by Visit

Parameter	Timepoint	Day 1	Day 28	Day 56	Unsch	Day 84	Day 112	Day 168 or EOS
	Study Day	**1**	**34**	**71**	**90**	**99**	**113**	**226**
FEV_1 (L)	Pre-dose	2.64	2.61	2.67	2.57	2.58	2.64	2.88
	Post-dose 5 min	1.81*	2.55	2.44	-	2.36	2.23	-
	%CFPDV	-31.4	-2.3	-8.6	-	-8.5	-15.5	
	Post-dose 30 min	2.54*	2.62	2.71	-	2.67	2.58*	-
	%CFPDV	-3.8	0.4	1.5	-	3.5	-2.3	
	Post-dose 1 h	2.46*	2.79	2.78	-	2.67	2.51*	-
	%CFPDV	-6.8	6.9	4.1	-	3.5	-4.9	
	Post-dose 2 h	2.62*	-	-	-	-	-	-
	%CFPDV	-0.8			-			
	Post-dose 4 h	2.41*	-	-	-	-	-	-
	%CFPDV	-8.7			-			
FVC (L)	Pre-dose	3.7	3.63	3.78	3.55	3.51	3.49	3.94
	Post-dose 5 min	2.76*	3.48	3.56	-	3.33	3.21	-
	Post-dose 30 min	3.63*	3.57	3.84	-	3.74	3.7*	-
	Post-dose 1 h	3.41*	3.68	3.78	-	3.64	3.55*	-
	Post-dose 2 h	3.51*	-	-	-	-	-	-
	Post-dose 4 h	3.41*	-	-	-	-	-	-
FEV_1/FVC	Pre-dose	0.71	0.72	0.71	0.72	0.74	0.76	0.73
	Post-dose 5 min	0.66*	0.73	0.69	-	0.71	0.69	-
	Post-dose 30 min	0.7*	0.73	0.71	-	0.71	0.70*	-
	Post-dose 1 h	0.72*	0.76	0.74	-	0.73	0.71*	-
	Post-dose 2 h	0.75*	-	-	-	-	-	-
	Post-dose 4 h	0.71*	-	-	-	-	-	-

%CFPDV=percent change from pre-dose to post-dose within a given visit; EOS=end of study; FEV_1=forced expiratory volume in 1 second; h=hour; min=minutes. FVC=forced vital capacity. *Denotes quality criteria were not met. '-' denotes not determined. Shaded cells across all spirometry parameters represent the timepoints for which reductions in FEV_1 were ≥10%.
Source: Listing 16.2.6.5

12.3.1.3 Other Narratives

12.3.1.3.1 PUR1900 40 mg Treatment Group

Subject ID: 102-002

A 32-year-old Asian female subject of childbearing potential was randomly assigned to the PUR1900 40 mg treatment group on 06 Feb 2023. Her height was 170.2 cm, weight was 82.6 kg, and BMI was 28.5 kg/m^2.

The subject's concomitant medications and concurrent medical conditions included salbutamol, fluticasone furoate/vilanterol, and montelukast sodium for asthma with Stage 2 ABPA; sertraline hydrochloride for anxiety, loratadine for perennial allergy; and ethinylestradiol/levonorgestrel for birth control.

On Day 83, the subject had a non-serious TEAE of mild oropharyngeal pain. Study drug administration was not changed. No treatment was provided. The investigator assessed the TEAE of mild sore throat as unrelated to the study drug and unrelated to the inhaler device. No alternate causality was provided. The event of mild sore throat resolved on Day 92.

There were no clinically significant findings in spirometry, vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram. There were no relative reductions from pre-dose FEV_1 values ≥10% at any time post dose across all visits.

The subject completed the treatment period on Day 116 (01 Jun 2023) and completed study participation on Day 169 (24 Jul 2023).

Subject ID: 202-001

An 18-year-old Asian male subject was randomly assigned to the PUR1900 40 mg treatment group on 12 Oct 2023. His height was 183.5 cm, weight was 67.0 kg, and BMI was 19.9 kg/m^2.

The subject's concomitant medications and concurrent medical conditions included azithromycin, budesonide/formoterol, ciclesonide, dupilumab, hypertonic saline solution, and salbutamol for asthma with Stage 5a ABPA, betamethasone dipropionate cream for eczema; loratadine for seasonal allergy; and doxycycline for acne prophylaxis.

No treatment-emergent adverse events (TEAEs) were reported for the subject.

There were no clinically significant findings in spirometry, vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram. There were no relative reductions from pre-dose FEV_1 values ≥10% at any time post dose across all visits.

The subject discontinued treatment early on Day 92 (11 Jan 2024) due to study termination by Sponsor. As a result of study termination, Subject 202-001 completed the Day 112/EOT assessments early on Day 92 and did not complete the Day 84 visit. The subject discontinued the

study early and completed the Day 168/EOS assessments on Day 135 (23 Feb 2024) due to study termination by Sponsor.

12.3.1.3.2 PUR1900 20 mg Treatment Group

Subject ID: 101-002

A 69-year-old white female was randomly assigned to the PUR1900 20 mg treatment group on 12 Sep 2023. Her height was 163.0 cm, weight was 52.0 kg, and BMI was 19.6 kg/m^2.

The subject's concomitant medications and concurrent medical conditions included salbutamol, azelastine, fluticasone furoate/vilanterol for asthma with Stage 4 ABPA, azithromycin for bronchiectasis, esterified estrogens, estradiol, and progesterone for menopause, fexofenadine/pseudoephedrine for seasonal allergy. Rosacea was another concurrent medical condition that was not associated with use of any concomitant medication. The subject also took vitamins and supplements including bifidobacterium infantis, biotin, fish oil, multivitamin/herbal supplement (Nutrafol), and prenatal vitamins. Other relevant past medical history included arthroscopy and meniscus operation for torn meniscus in 2013.

Subject 101-002 had 5 non-serious TEAEs, one of which was considered possibly related to study drug.

- On Day 9, the subject had a non-serious TEAE of mild pruritic rash (reported term: rash with itching on chest). Study drug administration was not changed. The investigator assessed the TEAE of mild pruritic rash to be possibly related to study drug and unrelated to the inhaler device. The event of mild pruritic rash resolved without concomitant or additional treatment on Day 29.
- On Day 116, the subject had a non-serious TEAE of moderate viral infection. The event was considered by the investigator to be unrelated to study drug and unrelated to the inhaler device. The event of moderate viral infection resolved on Day 124 with concomitant amoxicillin/clavulanic acid (PO BID on Days 120-129).
- On Day 140, the subject had a non-serious TEAE of mild arthralgia. The event was considered by the investigator to be unlikely related to study drug and unrelated to the inhaler device. The event of mild arthralgia was not resolved as of the last contact with the subject on Day 169.
- On Day 144, the subject had a non-serious TEAE of moderate viral infection. The event was considered by the investigator to be unrelated to study drug and unrelated to the inhaler device. The event of moderate viral infection resolved on Day 152 with concomitant azithromycin (PO three times per week on Days 144-152).
- On Day 162, the subject had a non-serious TEAE of mild back pain. The event was considered by the investigator to be unrelated to study drug and unrelated to the inhaler device. The event of mild back pain was not resolved as of the last contact with the subject on Day 169.

There were no clinically significant findings in spirometry, vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram. There were no reductions from pre-dose FEV_1 values ≥10% at any time post dose across all visits.

The subject completed the treatment period on Day 113 (02 Jan 2024) and completed the study on Day 169 (27 Feb 2024).

Subject ID: 102-006

A 66-year-old White female subject was randomly assigned to the PUR1900 20 mg treatment group on 09 May 2023. Her height was 162.6 cm, weight was 51.3 kg, and BMI was 19.4 kg/m^2.

The subject's concomitant medications and concurrent medical conditions included salbutamol, fluticasone furoate/vilanterol trifenatate for asthma with Stage 2 ABPA; thyroid for hypothyroidism; and sumatriptan for migraine.

Subject 102-006 had 2 non-serious TEAEs deemed unrelated to study drug.

- On Day 80, the subject had a non-serious TEAE of moderate asthma (reported term: asthma exacerbation). Study drug administration was not changed. The investigator assessed the TEAE of moderate asthma exacerbation to be unrelated to study drug and unrelated to the inhaler device. No alternate causality was provided. The event resolved on Day 84 without additional treatment.
- On Day 145, the subject had a non-serious TEAE of mild influenza. Study drug administration was not changed. The investigator assessed the TEAE of mild influenza to be unrelated to study drug and unrelated to the inhaler device. No alternate causality was provided. The event of moderate flu resolved on Day 153 with concomitant administration of oscillococcinum (homeopathic preparation) and paracetamol.

There were no clinically significant findings in vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram.

There were two instances of reductions in FEV_1 of ≥10% relative to pre-dose baseline at 5 minutes and 4 hours post-dose on Day 1. These declines were not associated with clinically significant respiratory symptoms. No other instances of reductions in FEV_1 of≥10% occurred post dose at any other visit. The subject's spirometry parameter pre- and post-dose values at each visit are presented in Table 4.

Table 4 Subject 102-006 Spirometry Parameters by Visit

Parameter	Timepoint	Day 1	Day 28	Day 56	Day 84	Day 112	Day 168 or EOS
	Study Day	**1**	**42**	**65**	**98**	**122**	**170**
FEV_1 (L)	Pre-dose	2.10	2.08	2.00	2.13	2.04	2.07
	Post-dose 5 min	1.82	1.97	2.07	2.11	2.12	-
	%CFPDV	-13.3	-5.3	3.5	-0.9	3.9	-
	Post-dose 30 min	1.99	2.04	1.98	2.15	2.10	-
	%CFPDV	-5.2	-1.9	-1.0	0.9	2.9	-
	Post-dose 1 h	2.05	2.12	2.02	2.13	2.14	-
	%CFPDV	-2.4	1.9	1.0	0.00	4.9	-
	Post-dose 2 h	1.98	-	-	-	-	-
	%CFPDV	-5.7	-	-	-	-	-
	Post-dose 4 h	1.89	-	-	-	-	-
	%CFPDV	-10.0	-	-	-	-	-
FVC (L)	Pre-dose	2.89	2.81	2.79	2.82	2.87	2.82
	Post-dose 5 min	2.54	2.68	2.85	2.77	2.79	-
	Post-dose 30 min	2.66	2.77	2.69	2.85	2.83	-
	Post-dose 1 h	2.75	2.84	2.75	2.83	2.96	-
	Post-dose 2 h	2.66	-	-	-	-	-
	Post-dose 4 h	2.56	-	-	-	-	-
FEV_1/FVC	Pre-dose	0.73	0.74	0.72	0.76	0.71	0.73
	Post-dose 5 min	0.72	0.74	0.73	0.76	0.76	-
	Post-dose 30 min	0.75	0.74	0.74	0.75	0.74	-
	Post-dose 1 h	0.75	0.75	0.73	0.75	0.72	-
	Post-dose 2 h	0.74	-	-	-	-	-
	Post-dose 4 h	0.74	-	-	-	-	-

%CFPDV=percent change from pre-dose to post-dose within a given visit; EOS=end of study; FEV_1=forced expiratory volume in 1 second; h=hour; min=minutes. FVC=forced vital capacity. '-' denotes not determined. Shaded cells across all spirometry parameters represent the timepoints for which reductions in FEV_1 were ≥10%.
Source: Listing 16.2.6.5

Subject 102-006 completed the treatment period on Day 122 (07 Sep 2023) and completed the study on Day 170 (25 Oct 2023).

Subject ID: 402-001

A 64-year-old post-menopausal white female was randomly assigned to the PUR1900 20 mg treatment group on 24 Oct 2023. Her height was 160.0 cm/ weight was 54.0 kg, BMI was 21.1 kg/m^2.

The subject's concomitant medications and concurrent medical conditions included fluticasone furoate/vilanterol and salbutamol for asthma with Stage 5a ABPA, bilastine and cromoglicate sodium for allergic conjunctivitis, and atorvastatin for dyslipidemia. Other concurrent medical conditions included adrenal insufficiency and mitral valve incompetence.

On Day 14, the subject had a non-serious TEAE of mild influenza like illness (verbatim: flu-like symptoms). Study drug administration was not changed. The subject was treated with paracetamol (1000 mg PO BID) on Day 14 and Day 15. The investigator assessed the TEAE of mild influenza like illness to be unrelated to study drug and unrelated to the inhaler device. The event resolved on Day 21.

There were no clinically significant findings in spirometry, vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram.

During study participation, there were 3 instances of reductions in FEV_1 of ≥10% from pre-dose values. On Day 28, post dose reductions of FEV_1 of -29.67%, -29.67% and -26.37% were observed at the 5-minute, 30-minute, and 1-hour timepoints, respectively. The subject did not have any clinically significant respiratory symptoms and study drug was not held because the pre-dose FEV_1 was deemed unreliable for the following reasons: 1) the pre-dose FEV_1 recorded on Da y 30 was ~0.80 L higher than the pre-dose FEV_1 recorded on Day 1 (2.73 L vs 1.91 L), suggesting that there may have been a technical problem with the pre-dose spirometry session and 2) the Day 30 pre-dose spirometry did not meet session acceptability criteria (failed QA) because there were zero acceptable or usable tests in this session. All tests had inspiration/expiration switched with upside down flow volume loops and volume time curves.

Post-dose FEV_1 values did not decline >2.6% at subsequent visits. The subject's spirometry parameter pre- and post-dose values at each visit are presented in Table 5.

Table 5 Subject 402-001 Spirometry Parameters by Visit

Parameter	Timepoint	Day 1	Day 28	Day 56	Day 112	Day 168 or EOS
	Study Day	**1**	**30**	**59**	**86**	**112**
FEV_1 (L)	Pre-dose	1.91	2.73*	1.95	1.83	1.98
	Post-dose 5 min	1.85*	1.92	1.90	1.84	-
	%CFPDV	-3.1	-29.7	-2.6	0.5	-
	Post-dose 30 min	1.98	1.92	1.91	1.82	-
	%CFPDV	3.7	-29.7	-2.1	-0.5	-
	Post-dose 1 h	1.96	2.01	1.90	1.84	-
	%CFPDV	2.6	-26.4	-2.6	0.5	-
	Post-dose 2 h	1.85	-	-	-	-
	%CFPDV	-3.1	-	-	-	-
	Post-dose 4 h	1.86	-	-	-	-
	%CFPDV	-2.6	-	-	-	-
FVC (L)	Pre-dose	2.85	2.78*	2.89	2.73	2.91
	Post-dose 5 min	2.7*	2.74	2.68	2.64	-
	Post-dose 30 min	2.77	2.78	2.71	2.74	-
	Post-dose 1 h	2.80	2.79	2.79	2.76	-
	Post-dose 2 h	2.77	-	-	-	-
	Post-dose 4 h	2.73	-	-	-	-
FEV_1/FVC	Pre-dose	0.67	0.98*	0.67	0.67	
	Post-dose 5 min	0.69*	0.70	0.71	0.70	-
	Post-dose 30 min	0.71	0.69	0.70	0.66	-
	Post-dose 1 h	0.70	0.72	0.68	0.67	-
	Post-dose 2 h	0.67	-	-	-	-
	Post-dose 4 h	0.68	-	-	-	-

%CFPDV=percent change from pre-dose to post-dose within a given visit; EOS=end of study; FEV_1=forced expiratory volume in 1 second; h=hour; min=minutes. FVC=forced vital capacity. *Denotes quality criteria were not met. '-' denotes not determined. Shaded cells across all spirometry parameters represent the timepoints for which reductions in FEV_1 were ≥10%.
Source: Listing 16.2.6.5

Subject 402-001 discontinued treatment early on Day 86 (17 Jan 2024) due to study termination by Sponsor. As a result of study termination, the subject completed the Day 112/EOT assessments early on Day 86 and did not complete the Day 84 visit. The subject was discontinued from the study early on Day 112 (12 Feb 2024) due to study termination by Sponsor.

12.3.1.3.3 Placebo Group

Subject ID: 101-001

A 61-year-old post-menopausal Asian female subject was randomly assigned to the placebo group on 31 Aug 2023. Her height was 162.0 cm, weight was 71.0 kg, and BMI was 27.1 kg/m^2.

The subject's concomitant medications and concurrent medical conditions included salbutamol, fluticasone furoate, budesonide, benralizumab, and fluticasone furoate/umeclidinium bromide/vilanterol trifenatate for asthma with Stage 4 ABPA; dapagliflozin for Type 2 diabetes mellitus; and nasal polyps. The subject underwent nasal polyp removal on Day 37.

Subject 101-001 had 9 non-serious mild TEAEs which were all considered unrelated to study drug.

- On Day 3 the subject had a non-serious TEAE of mild arthralgia (reported term: wrist pain). Study drug administration was not changed. The investigator assessed the TEAE of arthralgia to be unrelated to study drug and unrelated to the inhaler device. The TEAE was attributed to travel and the event resolved on Day 4.
- On Day 40, the subject had non-serious TEAEs of mild headache and mild nausea. Study drug administration was not changed. The investigator assessed each of these TEAEs to be unrelated to the study drug and unrelated to the inhaler device. The events of mild headache and mild nausea were attributed to the patient having nasal polyp removal surgery and resolved without treatment on Day 42.
- On Day 49, the subject had non-serious TEAEs of mild abnormal sputum and mild sputum discolored (verbatim terms: change in sputum consistency change in sputum color). Study drug administration was not changed. The investigator assessed each of these TEAEs to be unrelated to the study drug and unrelated to the inhaler device. The events were attributed to ABPA and resolved without treatment on Day 64.
- On Day 59, the subject had a non-serious TEAE of mild bacterial disease carrier (verbatim: nasal biopsy positive for Pseudomonas). Study drug administration was not changed. The investigator assessed the TEAE to be unrelated to study drug and unrelated to the inhaler device. The event resolved without treatment on Day 75.
- On Day 64, the subject had a non-serious TEAE of mild hypersensitivity (verbatim: allergy flare up). Study drug administration was not changed. The investigator assessed the TEAE to be unrelated to study drug and unrelated to the inhaler device. The event resolved without treatment on the same day (Day 64).
- On Day 110, the subject had a non-serious TEAE of mild oropharyngeal pain. Study drug administration was not changed. The investigator assessed the TEAE to be unrelated to study drug and unrelated to the inhaler device. The event resolved without treatment on Day 111.
- On Day 113, the subject had a non-serious TEAE of epistaxis. The investigator assessed the TEAE to be unrelated to study drug and unrelated to the inhaler device. The event

was attributed to the subject preforming spirometry and resolved on the same day (Day 113).

There were no clinically significant findings in spirometry, vital sign measurements, physical examination, clinical laboratory tests, or 12-lead electrocardiogram. During study participation, there were no instances of reductions in FEV_1 of >10% at any time point post-dose across all visits.

The subject completed the treatment period on Day 113 (21 Dec 2023). The subject completed study participation on Day 169 (15 Feb 2024).

12.4 Clinical Laboratory Evaluation

There were no clinically significant abnormal laboratory values (Table 14.3.4.1 and Table 14.3.4.2).

There were no notable mean changes from baseline in hematology, chemistry, or urinalysis parameters over time. Table 14.3.7.1 summarizes hematology values and change from baseline over time for the safety analysis set. Table 14.3.7.2 summarizes chemistry values and change from baseline over time for the safety analysis set. Table 14.3.7.3 summarizes urinalysis values and change from baseline over time for the safety analysis set.

There were no clinically significant changes in laboratory values in individual subjects. Hematology values are listed by subject in Listing 16.2.8.1. Chemistry values are listed by subject in Listing 16.2.8.2. Urinalysis values are listed by subject in Listing 16.2.8.3.

There were no cases of potential Hy's law (defined as alanine aminotransferase or aspartate aminotransferase ≥ three times upper limit of normal [ULN], total bilirubin greater than or equal to 2 times ULN, and alkaline phosphatase less than 2 times ULN) (Listing 16.2.8.4).

12.5 FEV_1 Monitoring, Vital Signs, Physical Exams, and Other Observations Related to Safety

12.5.1 FEV_1 Monitoring

Overall, 4 subjects (PUR1900 20 mg [n=2], PUR1900 40 mg [n=1], placebo-treated [n=1]) experienced at least 1 instance of a relative decline in forced expiratory volume in 1 second (FEV_1) ≥10% compared to the pre-dose FEV_1 value.

Subjects who experienced a relative decline in FEV_1 of >20% compared to pre-dose FEV_1 value were to be evaluated and treated according to standard medical practice and study drug was to be held for at least 7 days per protocol.

Three subjects had a >20% relative decline in FEV1 at ≥1 post-dose time point during the study:

- Subject 402-001 (PUR1900 20 mg): 26-30% relative decline in FEV_1 was observed at all 3 post-dose time points (5 min, 30 min, 1 hour) on Day 30. Study drug was not held

because the pre-dose FEV_1 was deemed unreliable for the reasons described below. Post-dose FEV_1 values did not decline >2.6% at subsequent visits.

1. The pre-dose FEV_1 recorded on Day 30 was ~0.80 L higher than the pre-dose FEV_1 recorded on Day 1 (2.73 L vs 1.91 L), suggesting that there may have been a technical problem with the pre-dose spirometry session.
2. The Day 30 pre-dose spirometry did not meet session acceptability criteria (failed QA) because there were zero acceptable or usable tests in this session. All tests had inspiration/expiration switched with upside down flow volume loops and volume time curves.

- Subject 102-001 (PUR1900 40 mg): 31.4% relative decline in FEV_1 was observed at 5 min post-dose on Day 1. Study drug was not held. Post-dose FEV_1 recorded at 30 min, 1 hour, 2 hour, and 4 hours were -3.8%, -6.8%, -0.8%, and -8.7% relative to the pre-dose FEV_1 on Day 1. FEV_1 values did not decline >15.5% at subsequent visits.
- Subject 107-001 (placebo): 20.9% relative decline in FEV1 was observed at 5 min post-dose on Day 34. Study drug was held per protocol. The subject was rechallenged on Study Day 43 and the maximum decrease in FEV_1 observed post-dose was 11.2% and the subject was restarted on study drug. The subject was subsequently discontinued from study drug on Day 47 due to a moderate cough deemed possibly related to study drug.

Spirometry parameters pre- and post-dose at each visit are presented for each subject with at least 1 instance of a relative decline in FEV_1 ≥10% compared to the pre-dose FEV_1 value in the narratives in Section 12.3.1.

Spirometry data are listed by subject in Listing 16.2.6.5.

12.5.2 Vital Signs

There were no important findings in vital sign parameters.

Vital sign parameters are described by subject in Listing 16.2.8.5.

12.5.3 Physical Findings

There were no important physical examination findings.

Physical examination findings are described by subject in Listing 16.2.8.7.

12.5.4 Electrocardiogram Findings

There were no clinically significant electrocardiogram findings.

QTcF values of potential clinical concern are summarized in Table 14.3.7.4.

There was 1 subject with an increase in QTcF ≥ 30 millisecond (ms): Subject 402-001 (PUR1900 20 mg) average QTcF at baseline (Screening), Day 28, and Day 112 was 398 ms, 410 ms, and 428 ms, respectively, representing a 30 ms increase at Day 112.

There was 1 subject with QTcF >450 ms observed post-baseline: Subject 102-006 (PUR1900 20 mg) average QTcF at baseline (Screening), Day 28, and Day 112 was 445 ms, 429 ms, and 454 ms, respectively.

Electrocardiogram findings are described by subject in Listing 16.2.8.6.

12.5.5 Other Observations Relevant to Safety

In-home safety monitoring included use of an asthma monitoring device (AMD) to record peak expiratory flow rate (PEFR), study drug administration, respiratory/asthma symptoms, and use of bronchodilator rescue medication at home. PEFR data collected on the AMD are described by subject in Listing 16.2.8.8.

No pregnancies were reported (Listing 16.2.8.9).

13 DISCUSSION AND OVERALL CONCLUSIONS

Mild to moderate respiratory symptoms including asthma exacerbations and oropharyngeal pain, as well as mild arthralgia were the most common TEAEs reported overall. Asthma exacerbations were reported in 2 PUR1900-treated subjects, while oropharyngeal pain and arthralgia were reported in one subject each in PUR1900 and placebo-treated subjects. All other TEAEs were reported in one subject each, preventing any comparison across treatment groups. There were no SAEs or deaths. One subject in the placebo group discontinued treatment early due to moderate increased cough.

Transient declines in FEV_1 were observed as early as 5 minutes post-dose in 3 PUR1900-treated and 1 placebo-treated subject. These declines appeared to be reversible and were not associated with clinically significant respiratory symptoms.

No significant changes or abnormalities were observed in laboratory results, ECGs, physical examinations, or vital signs.

Due to the small number of subjects in the dosing groups, no conclusions can be drawn from these data.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Table 14.1.1 Subject Disposition - Screened Set

Table 14.1.2 Demographics and Baseline Characteristics - Safety Analysis Set

Table 14.1.3.1 Medical History Ongoing at Screening by System Organ Class and Preferred Term - Safety Analysis Set

14.2 Efficacy Endpoints

No summary tables were produced. Efficacy endpoints are listed by subject.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Study Drug Exposure and Overall Compliance - Safety Analysis Set

Table 14.3.1.2 Overall Summary of Adverse Events - Safety Analysis Set

Table 14.3.1.3 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Analysis Set

Table 14.3.7.1 Hematology Data, Descriptive Statistics for Observed Values and Change from Baseline - Safety Analysis Set

Table 14.3.7.2 Chemistry Data, Descriptive Statistics for Observed Values and Change from Baseline - Safety Analysis Set

Table 14.3.7.3 Urinalysis Data, Descriptive Statistics for Observed Values and Change from Baseline - Safety Analysis Set

Table 14.3.7.4 QTcF values of Potential Clinical Concern Any Time, Post-Baseline by Category - Safety Analysis Set

Table 14.3.8.1 Concomitant Medications by Anatomical Therapeutic Chemical and Drug Name Safety Analysis Set

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1 Listing of Serious Adverse Events and Adverse Events Leading to Death or Discontinuation of Treatment - Safety Analysis Set

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

There were no deaths or SAEs. One subject (107-001 in placebo arm) had a TEAE leading to treatment discontinuation and one subject (102-001 in PUR1900 40 mg arm) had an AECI.

Brief narratives are included in Section 12.3.1 for all 8 subjects regardless of occurrence of SAEs, TEAEs leading to treatment discontinuation, or AECIs.

14.3.4 Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Listing of Abnormal Laboratory Values – Safety Analysis Set

Table 14.3.4.2 Laboratory Data, Clinically Significant Laboratory Parameters Any Time, Post-Baseline - Safety Analysis Set

15 REFERENCES

1. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88. doi:10.1164/rccm.201908-1590st

16 APPENDICES

16.1.1 Protocol and Protocol Amendments:

Protocol Version 1.1

Protocol Version 1.2 (UK only)

Protocol Version 2.0

Clarification memos

16.1.2 Sample Case Report Form (unique pages only)

16.1.5 Signature of Sponsor's Responsible Medical Officer

16.1.9 Statistical Analysis Plan

16.2.6 Individual Efficacy endpoints Response Data

16.2.7 Adverse Event Listings

16.2.8 Listings of Individual Laboratory Measurements by Subject

16.3.1 Case Report Forms for deaths, other serious AEs and withdrawals for AE

16.4 Individual Patient Data Listings